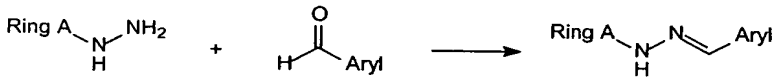
their effects on the prototheramutein- and theramutein-expressing cell lines. Compound 3 (C3) shows the best example of the ability of the method to identify a compound that exerts an even greater effect on the theramutein than on its corresponding prototheramutein. (Panel E). Panel A: control DMSO treatments; B: negative heterologous specificity gap; C: slightly positive heterologous specificity gap; D: large positive homologous specificity gap; E: positive heterologous specificity gap. See text for explanations.—

On page 15, please delete paragraph [0041] and replace with the following paragraph:

-- An important component and conceptual teaching of the Invention described herein is that neither the R^2 nor the R^3 positions of the compounds of this invention are members of any aromatic or non-aromatic ring structure. We have discovered that compounds having the R^2 and/or the R^3 positions as members of any aromatic or non-aromatic ring structure do not effectively inhibit the T315I theramutein, whereas the compounds of the invention that lack such a ring component at these positions, in addition to having other preferred chemical groups, are potent inhibitors of the T315I theramutein.—

On page 42, please delete paragraph [0072] and replace with the following paragraph:

--Embodiments wherein R^2 = NH, R^3 = N, R^4 = CH, and R^5 = -aryl may be prepared by reaction of an appropriate hydrazine compound, such as ***A***, and an appropriate aldehyde, such as ***B***, under conditions similar to those described on p. 562 of Gineinah, *et al.* (Arch. Pharm. Pharm. Med. Chem. **2002**, 335, 556-562).

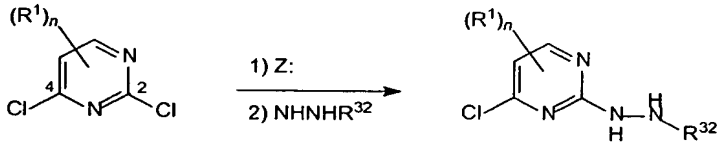


A ***B*** ***C***

For example, heating ***A*** with 1.1 equivalents of ***B*** for 1 to 24 hours in a protic solvent such as a C_1 to C_6 alcohol, followed by cooling and collection of the precipitate, would afford ***C***. Alternatively, product ***C*** may be isolated by evaporation of the solvent and purification by chromatography using silica gel, alumina, or C_4 to C_{18} reverse phase medium. Similar methodology would be applicable in the cases where "Aryl" is replaced by other groups defined under R^5.--

On page 43, please delete paragraph [0074] and replace with the following paragraph:

-- Precursors such as ***A*** and ***D*** may be prepared by reaction of an appropriate nucleophile, for example, a hydrazine derivative, with a heteroaromatic compound bearing a halo substituent at a position adjacent to a nitrogen atom. For example, using methods analogous to those described by Wu, *et al.* (J. Heterocyclic Chem. **1990**, 27, 1559-1563), Breshears, *et al.* (J. Am. Chem. Soc. **1959**, 81, 3789-3792), or Gineinah, *et al.* (Arch. Pharm. Pharm. Med. Chem. **2002**, 335, 556-562), examples of compounds ***A*** and ***D*** may be prepared starting from, for example, a 2,4-dihalopyrimidine derivative, many of which are commercially available or are otherwise readily prepared by one skilled in the art. Thus, treatment of an appropriate 2,4-dihalopyrimidine derivative ***G*** with an amine or other nucleophile (Z), optionally in the presence of an added base, selectively displaces the 4-halo substituent on the pyrimidine ring. Subsequent treatment of the product with a second nucleophilic reagent such as hydrazine or a hydrazine derivative, optionally in a solvent such as a C_1 to C_6 alcohol and optionally in the presence of an added base, displaces the 2-halo substituent on the pyrimidine ring, to afford compounds that are examples of structures ***A*** and ***D*** above.



G

On page 50, please delete paragraph [0093] and replace with the following paragraph:

-- As used herein, the terms "agonist" and "activator" of a protein are used interchangeably. An activator (agonist) is limited to a substance that binds to and activates the functioning of a given protein. Unless explicitly stated otherwise, an "activator", an "agonist", and an "activator of a protein" are identical in meaning. The activation by an activator may be partial or complete. Likewise, as used herein, the terms "antagonist" and "inhibitor" of a protein are used interchangeably. An inhibitor (antagonist) is limited to a substance that binds to and inhibits the functioning of a given protein. To state that a substance "inhibit(s)" a protein means the substance binds to the protein and reduce(s) the protein's activity in the cell without materially reducing the amount of the protein in the cell. Similarly, to state that a substance "activate(s)" a protein, such as a

prototheramutein or theramutein, is to state that the substance increased the defined function of the protein in the cell without substantially altering the level of the protein in the cell. Unless explicitly stated otherwise, an "inhibitor", an "antagonist" and an "inhibitor of a protein" are also synonymous. The inhibition by an inhibitor may be partial or complete. A modulator is an activator or an inhibitor. By way of example, an "activator of $PKC_{\beta I}$" should be construed to mean a substance that binds to and activates $PKC_{\beta I}$. Similarly, an "inhibitor of $p210^{Bcr\text{-}Abl}$" is a substance that binds to and inhibits the functioning of $p210^{Bcr\text{-}Abl}$. To state that a substance "inhibits a protein" requires that the substance bind to the protein in order to exert its inhibitory effect. Similarly, to state that a substance "activates protein X" is to state that the substance binds to and activates protein X. The terms "bind(s)," "binding," and "binds to" have their ordinary meanings in the field of biochemistry in terms of describing the interaction between two substances (*e.g.*, enzyme-substrate, protein-DNA, receptor-ligand, etc.). As used herein, the term "binds to" is synonymous with "interacts with" in the context of discussing the relationship between a substance and its corresponding target protein. As used herein, to state that a substance "acts on" a protein, "affects" a protein, "exerts its effect on" a protein, etc., and all such related terms uniformly mean (as the skilled investigator is well aware) that said substance activates or inhibits said protein.—

On page 51, please delete paragraph [0096] and replace with the following paragraph:

-- Alternatively, when a comparison is made between the effects of two distinct substances (generally, but not always), one of which is tested on the theramutein and the other on the prototheramutein, respectively, the result is termed a ***heterologous specificity gap*** **(SG)** determination. Thus, (a) and (c) as given above are examples of heterologous specificity gap (SG) determinations (although (a) uses the same substance in both instances), whereas (b) is an example of a homologous specificity gap determination.—

On page 54, please delete paragraph [0109] and replace with the following paragraph:

-- Indeed, prior to the disclosure of this invention, including both the detailed methodology described for the first time herein as well as the compositions provided herein, *no one anywhere in the world* has been successful in identifying a chemical agent, let alone a methodology that is capable of identifying a chemical agent that effectively inhibits the $p210^{Bcr\text{-}AblT315I}$

theramutein to an equal or greater extent than STI-571 is able to do with respect to the wild type $p210^{Bcr\text{-}Abl}$ protein. (See Shah et al., Science, July, 2004; O'Hare et al., Blood, 2004; Tipping et al., Leukemia, 2004; Weisberg et al., Leukemia, 2004).—

On page 58, please delete paragraph [0118] and replace with the following paragraph:

--Preferably, the theramutein is stably expressed in a test cell. Stable expression results in a level of the theramutein in the cell that remains relatively unchanged during the course of an assay. For example, stimulation or activation of a component of a signaling pathway may be followed by a refractory period during which signaling is inhibited due to down-regulation of the component. For theramuteins of the invention, such down-regulation is usually sufficiently overcome by artificially overexpressing the theramutein. Expressed another way, the expression is sufficiently maintained that changes in a phenotypic characteristic that are observed during the course of an assay are due primarily to inhibition or activation of the theramutein, rather than a change in its level, even if down-modulation of the theramutein subsequently occurs. For these reasons, although stable expression of the theramutein is preferred, transfection followed by transient expression of the theramutein may be employed provided that the selected phenotypic characteristic is measurable and the duration of the assay system is short relative to the progressive decline in the levels of the transiently expressed theramutein which is to be expected in such systems over time. For these reasons, stably expressing cell lines are preferred (U.S. Patent No. 4,980,281).--

On page 60, please delete paragraph [0122] and replace with the following paragraph:

--3) Provision of a control cell that expresses the prototheramutein corresponding to the theramutein of interest. As some of the muteins that are described herein are also enzymes, they usually retain catalytic activity, and therefore the control cell usually displays substantially the same phenotypic characteristic as the test cell. The phenotypic characteristic need not be quantitatively alike in both cells, however. For example, a mutation that leads to reactivation of the prototheramutein may also increase, decrease, or otherwise affect its specific activity with respect to one or more of its substrates in the cell. As a result, it may exhibit the selected phenotypic characteristic to a greater or lesser extent. Accordingly, it may be desirable in some cases to adjust expression

of either or both of the prototheramutein and the theramutein such that test and control cells exhibit the phenotypic characteristic to approximately the same degree. This may be done, for example, by expressing the proteins from promoters whose activity can be adjusted by adjusting the amount of inducer present, all using standard methodology (see, for example, Sambrook et al. 1989 & 2001).—

On page 61, please delete paragraph [0124] and replace with the following paragraph:

-- Alternatively, the skilled investigator may also wish to use unmodified host cells or host cells harboring the expression vector only as control cells for certain experimental procedures. (The host cells are the cells into which an expression vector encoding the theramutein was introduced in order to generate the test cells.) This may be the case where the investigator is only interested in identifying a specific inhibitor or activator of the theramutein of interest, irrespective of whether or not said compound is also effective against the prototheramutein of interest (pTOI).--

On page 65, please delete paragraph [0138] and replace with the following paragraph:

-- Other examples of growth factor receptors involved in tumorigenesis are the receptors for vascular endothelial growth factor (VEGFR-1 and VEGFR-2), platelet-derived growth factor (PDGFR), nerve growth factor (NGFR), fibroblast growth factor (FGFR), and others.—

On page 66, please delete paragraph [0140] and replace with the following paragraph:

-- In the present invention, any suitable method or route can be used to administer theramutein inhibitors of the invention, and optionally, to co-administer anti-neoplastic agents and/or antagonists of other receptors. The anti-neoplastic agent regimens utilized according to the invention, include any regimen believed to be optimally suitable for the treatment of the patient's neoplastic condition. Different malignancies can require use of specific anti-tumor antibodies and specific anti-neoplastic agents, which will be determined on a patient to patient basis. Routes of administration include, for example, oral, intravenous, intraperitoneal, subcutaneous, or intramuscular administration. The dose of antagonist administered depends on numerous factors, including, for example, the type of antagonists, the type and severity of the tumor being treated

and the route of administration of the antagonists. It should be emphasized, however, that the present invention is not limited to any particular method or route of administration.—

On page 70, please delete paragraph [0152] and replace with the following paragraph:

-- All five compounds inhibited $p210^{Bcr\text{-}Abl\text{-}T315I}$ 120 Kd activity as measured by inhibition of autophosphorylation activity, as shown in Figure 4. Thus, of the 6 highest scoring compounds out of more than 113,000 compounds screened, at least 5 of the six directly inhibited the $p210^{Bcr\text{-}Abl\text{-}T315I}$ mutant. It is noteworthy that Compound 5 appears to spread the recombinant protein band out on the SDS page gel. This was also evident on the silver-stained gel (data not shown). It is possible that this compound may actually be a "suicide" inhibitor that is able to covalently cross-link the POI in order to permanently inhibit its activity, but this will require further study.--

Enclosed are replacement sheets 8, 9, 15, 42, 43, 50, 51, 54, 58, 60, 61, 65 66, 70, and 72 through 75b.